REMARKS

Upon entry of the present amendment, claims 1, 3, 19 and 21-23 are canceled, claims 2, 5-8, 12-18, and 20 are amended and claim 24 is newly presented. Accordingly, claims 2, 4-18, 20 and 24 directed to a process for purifying wild-type von Willebrand factor (VWF) from a plasma fraction using non-binding hydroxyapatite chromatography are presently pending.

In an effort to expedite prosecution, Applicants have canceled claim 1 and amended claim 2 to specify that "wild-type" von Willebrand factor (VWF) (as opposed to recombinant VWF and fragments thereof) is recovered from a "plasma fraction" starting material by means of "flow" (i.e., non-binding) chromatography with hydroxyapatite, "under conditions that permit at least one contaminating protein to bind to the hydroxylapatite matrix while VWF is substantially not bound to the hydroxylapatite matrix". Thus, the unbound VWF may be collected in a "flow through fraction". Applicants respectfully submit that support for the claims as amended herewith is found in the specification as originally filed, for example at:

- Page 5, lines 4-5 ("This embodiment is referred to as 'flow chromatography' in the present application.");
- Page 9, lines 15-18 ("In a particular embodiment, a flow chromatography with hydroxylapatite is initially carried out, VWF not binding to the hydroxylapatite matrix, and then the flow fraction is re-chromatographed under binding conditions and the VWF fraction is eluted."); and
- Page 11, line 8 ("wild-type VWF") and lines 26-27 ("plasma fraction").

Applicants submit that no new matter has been added. However, Applicants reiterate that the amendments herein are presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Applicants further submit that the invention embodied by the pending claims is distinct from the cited prior art of record. Accordingly, reconsideration and withdrawal of the outstanding grounds of rejection is respectfully requested in view of the amendments and

remarks presented herewith.

Oath/Declaration

The Examiner asserts that the oath is defective because the "foreign priority information is missing". Applicants wish to remind the Examiner that pursuant to 37 C.F.R. § 1.63(c)(2), such information may be supplied in an application data sheet separately filed in accordance with 37 C.F.R. § 1.76. To that end, Applicants direct the Examiner's attention to page 2 of the Application Data Sheet submitted with the original application on September 26, 2006. Accordingly, Applicants respectfully submit that the Examiner's objection is misplaced and respectfully petition for the withdrawal thereof.

Filing Receipt Correction

Applicants note that the filing date of the instant application is still erroneously listed as June 22, 2007. As noted in the Request for Corrected Filing Receipt submitted September 24, 2007, the instant application was complete as of the September 26, 2006 submission and thus the correct filing or 371(c) date is September 26, 2006. Accordingly, Applicants respectfully petition for action on their Request of September 24th and the issuance of a corrected filing receipt in due course.

Claim Objections

The Examiner objected to claims 1-20 and 22-23 for containing certain informalities. At the outset, Applicants wish to point out than claims 1, 3, and 22-23 are canceled herewith, thereby rendering moot any objections thereof. As for the remaining objections to claims 2 and 13:

- Claim 2 has been amended to specify "A process for purifying wild-type von Willebrand factor (VWF) from a plasma fraction comprising steps of. . .".; and

- Claim 13 has been amended to specify that the "flow through fraction containing unbound VWF" set forth in claim 2 is re-chromatographed under binding conditions and the VWF fraction is eluted.

Applicants submit that the amendments and remarks presented herewith render moot the Examiner's objections. Accordingly, Applicants respectfully petition for the withdrawal thereof.

Rejections Under 35 USC 112, Second Paragraph

The Examiner rejected claims 1, 5-20, and 22-23 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim that which Applicants regard as the invention. At the outset, Applicants wish to again point out than claims 1 and 22-23 are canceled herewith, thereby rendering moot any rejection thereof. As for the remaining rejections to claims 5 and 6:

- Applicants have canceled the "preferably" clause from claim 5 and represented the preferred pH range of 6.8 to 7.5 in new claim 24; and

- Applicants have amended claim 6 to refer to "a running buffer in the flow chromatography".

Applicants submit that the amendments and remarks presented herewith render moot the Examiner's rejections under section 112, second paragraph. Accordingly, Applicants respectfully petition for the withdrawal thereof.

Rejections Under 35 USC 112, First Paragraph

The Examiner rejected claims 1-20 and 22-23 under 35 U.S.C. § 112, first paragraph, for failing the written description and enablement requirements. According to the Examiner, the recited term "VWF" encompasses *any* VWF, of unlimited structure and function, from *any* source, and including fragments, variants and recombinants thereof. As such, the claim scope exceeds the enabling support and description of the as-filed specification.

At the outset, Applicants wish to again point out than claims 1, 3, and 22-23 are canceled herewith, thereby rendering moot any objections thereof. As for the remaining rejections, although Applicants respectfully disagree with the Examiner's characterization of the claimed subject matter as beyond the scope of the originally filed specification, Applicants have nevertheless restricted the claims to "wild-type von Willebrand factor (VWF)" in an effort to expedite prosecution.

Applicants submit that the amendments and remarks presented herewith render moot the Examiner's rejections under section 112, first paragraph. Accordingly, Applicants respectfully petition for the withdrawal thereof.

Rejections Under 35 USC 102

The Examiner rejected claims 22-23 under 35 U.S.C. § 102(b) as being anticipated by Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pp. 1-11). Applicants respectfully submit that this rejection is rendered moot by the cancelation of claims 22-23 and thus respectfully petitions for the withdrawal thereof.

The Examiner rejected claims 1-3, 5-11, 12, 14 and 22-23 under 35 U.S.C. § 102(b) as being anticipated by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pp. 341-352) and claims 1-3, 5-12 and 22-23 under 35 U.S.C. § 102(b) as being anticipated by Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pp. 23327-23334).

At the outset, Applicants wish to point out than claims 1 and 3 are canceled herewith, thereby rendering moot any objections thereof. As for the remaining rejections, Applicants wish to remind the Examiner that anticipation requires that a single reference disclose each and every element of the claim. In this case, Applicants respectfully disagree with the Examiner's characterization of the prior art teachings and respectfully submit that the invention of the pending claims in novel in view thereof. Specifically:

The Gorman reference describes the purification of human antihaemophilic factor (factor VIII) using binding chromatography, in contrast to the flow chromatography of the instant invention. In particular, Gorman et al. teach the step of loading a precipitated and gel-filtered plasma preparation onto a hydroxylapatite column, washing the column with an equilibration buffer and then simultaneously eluting factor VIII and VWF with a gradient from 5 mM to 500 mM potassium phosphate buffer (pH 6.8). See page 343, second paragraph. Thus, Gorman expressly discloses a process wherein VWF is first bound to the hydroxylapatite column.

In contrast, claim 2 as amended herewith expressly requires the steps of "(i) carrying out flow chromatography with hydroxyapatite. . .under conditions that permit at least one contaminating protein to bind to the hydroxylapatite matrix while VWF is substantially not bound to the hydroxylapatite matrix" and "(ii) collecting a flow through fraction containing

unbound VWF". Accordingly, since Gorman fails to disclose the use of non-binding "flow" hydroxylapatite chromatography to purify VWF from a plasma fraction, Applicants respectfully submit that it cannot be fairly characterized as anticipating the invention of the pending claims.

The Dumas disclosure is similarly deficient. In contrast to the instant invention, directed to the purification of wild-type VWF from plasma fractions, the Dumas teachings are limited to the purification of recombinant VWF fragments. As such, the Dumas reference cannot be fairly characterized as anticipating the invention of the pending claims.

In sum, Applicants respectfully submit that neither Gorman nor Dumas disclose each and every element of the pending claims and thus cannot be fairly characterized as anticipating the invention of the pending claims. Accordingly, Applicants respectfully petition for reconsideration and withdrawal of anticipation rejections in view of the amendments and remarks herein.

Rejections Under 35 USC 103

The Examiner presented a number of obviousness grounds of rejection, including:

- The rejection of claims 1-17, 19 and 22-23 under 35 U.S.C. § 103(a) as obvious over Burnouf-Radosevich et al. or Newman et al., in view of Labrou, Dumas et al., and Zardi et al.;
- The rejection of claims 18 and 20 under 35 U.S.C. § 103(a) as obvious over Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas and Zardi et al., further in view of Winkelman and Ichitsuka et al.; and
- The rejection of claim 13 under 35 U.S.C. § 103(a) as obvious over Burnouf-Radosevich et al. or Newman et al., in view of Labrou, Dumas et al., Zardi et al, Winkelman and Ichitsuka et al., further in view of Daniel Marshak and Schroder et al.

At the outset, Applicants wish to again point out than claims 1, 3 and 22-23 have been canceled herewith, thereby rendering moot any objections thereof. As for the remaining rejections, Applicants wish to remind the Examiner that *prima facie* obviousness requires (1)

some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) the teaching or suggestion of all the claim limitations, and (3) a reasonable expectation of success. In the instant case, Applicants respectfully disagree with both the Examiner's characterization of the prior art teachings and her conclusions of obviousness and further submit that the invention of the pending claims in patentable over the cited disclosures. Nevertheless, in an effort to expedite prosecution, Applicants have herewith amended independent claims 2 to require a "process for purifying wild-type von Willebrand factor (VWF) from a plasma fraction" including the steps of "(i) carrying out flow chromatography with hydroxyapatite by contacting a plasma fraction containing wild-type VWF and one or more contaminating proteins with a hydroxylapatite matrix under conditions that permit at least one contaminating protein to bind to the hydroxylapatite matrix, while VWF is substantially not bound to the hydroxylapatite matrix" and "(ii) collecting a flow through fraction containing unbound VWF". Applicants respectfully submit that none of the prior art references of record disclose or suggest this novel configuration or its resulting improvement. Accordingly, any combination of references will necessarily fail to teach or suggest all the claim limitations and thus cannot be fairly characterized as obviating the invention of the pending claims. To that end, Applicant offers the following comments:

The present invention is based on the surprising finding that one can use "flow" or "non-binding" HA chromatography, optionally in conjunction with traditional "binding" HA chromatography, to remove a significant portion of undesired proteins from a plasma fraction and thereby yield a VWF of surprisingly high purity. Neither Applicants' process nor Applicants' result is fairly disclosed by the cited prior art references, applied alone or in combination. For example, Dumas reference discloses the use of a hydroxylapatite column to purify the A1 domain of VWF. The A1 domain is only a small portion of the complete amino acid sequence of VWF, namely residues 496-709 of the mature VWF subunit (see page 23328, left column, last paragraph, first line of Dumas). A person skilled in the art would not have reasonably expected that a purification process established for the single isolated domain of a protein could be successfully applied to the whole protein *mutatis mutandis*. Contrary thereto, domains are often purified because the whole protein cannot be purified. This is not surprising, as isolated domains often have different physical

properties than the full length proteins. In addition, Dumas only discloses binding hydroxylapatite chromatography in which VWF is initially bound to the hydroxylapatite matrix and only subsequently eluted. Contrary thereto, the present invention requires non-binding hydroxylapatite chromatography in which unbound VWF is found in the flow through. For these reasons, Dumas is only of passing interest and cannot be fairly characterized as obviating the invention of the pending claims, either on its own or in combination with other references.

Neither Burnouf-Radosevic et al. nor Newman et al. teach a purification method using hydroxylapatite. The examiner therefore cites to Labrou, Dumas, and Zardi in order to cure this deficiency. However, all three references only very generally describe hydroxylapatite chromatography. None mentions or suggests VWF, not do they mention the particular utility of non-binding hydroxylapatite chromatography in the context of purifying VWF. The Examiner's comment that Labrou teaches that hydroxylapatite is "unique in achieving the high standards of product purity dictated by the regulatory authorities for commercial bioproducts" is incorrect, as Labrou only states that "chromatography" in general is unique in achieving the high standards of product purity. Thus, when given their proper context and interpretation, the supplemental Labrou, Dumas, and Zardi are only of limited interest.

Assuming, *arguendo*, that the skilled person would be motivated to combine the diverse and disparate teachings of Burnouf-Radosevic and Newman with those of Labrou, Dumas and Zardi, such a combination would nevertheless not render obvious the use of a non-binding flow hydroxylapatite chromatography for VWF purification, i.e. a chromatography wherein VWF is loaded onto the column under non-binding conditions such that it can be found in the flow through. At the time of invention, this type of chromatography was entirely unusual, at least with respect to VWF.

On this issue and with particular reference to dependent claims 7 and 13 *et seq.*, the Examiner seems to suggest that the Marshak and Schröder references can readily cure the deficiencies of seven other references. However, like the seven before it, these two references also fail to teach hydroxylapatite chromatography for VWF, much less non-binding HA chromatography for VWF purification. For example, the cited passage of Marshak refers to the purification of calmodulin by DEAE-cellulose chromatography. Given that the cited passage refers to a different protein and to a different chromatography material, it has no bearing on the

obviousness of the present invention. Moreover, it is difficult to see how this passage can be fairly characterized as suggesting that one carry out a hydroxylapatite chromatography under conditions where VWF does not bind to the column as the pending claims require. In a similar fashion, the fact that Schröder teaches that the adsorption of proteins to hydroxylapatite is complicated because it involves both anionic and cationic exchange (left column, lines 11-12) has no bearing on whether it would be obvious to use non-binding HA chromatography to purify wild-type VWF from a plasma fraction.

In sum, Applicants respectfully submit that it is incumbent upon the Examiner to consider the invention as a whole and that it is improper to arbitrarily pick and choose among disparate reference, cobbling together passages taken out of context, to arrive at a conclusion of obviousness. In any event, Applicants respectfully submit that none of the nine cited prior art references, alone or in combination, fairly disclose or suggest the invention of the pending claims, including each and every element of the pending claims, with any reasonable degree of predictability. Accordingly, Applicants respectfully petition for reconsideration and withdrawal of obviousness rejections in view of the amendments and remarks herein.

Double Patenting

Claims 1-20 stand rejected on the grounds of obviousness-type double patenting for being obvious over claims 4-6, 8-17, and 26-27 of U.S. Patent No. 7,659,247 (issued from USSN 10/594,454). Applicants wish to point out that a terminal disclaimer referencing the instant application was previously submitted in the '454, in the response filed September 29, 2009. Thus, Applicants submit that this rejection is now moot and accordingly request withdrawal of thereof.

Claims 1-18 stand further rejected on the grounds of obviousness-type double patenting, albeit provisionally, for being obvious over claims 2, 4-15, 17, and 24 of co-pending application Serial No. 10/594,453. While Applicants disagree with the Examiner's characterization of the overlapping subject matter and her conclusion of obviousness, they nevertheless will consider the submission of a terminal disclaimer to expedite prosecution. However, Applicants wish to hold in abeyance such a filing until the claims of the instant application are otherwise in condition for

allowance.

CONCLUSION

The Office Action of **January 15, 2010** set a three-month shortened statutory period for response. Pursuant to the entry of Applicants' petition for three-month extension of time, response is due on or before **July 15, 2010**. Accordingly, Applicants submit that this response is timely and no additional fees, apart from those included herewith, are required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: **July 15, 2010**

By: **/chalin a. smith/**

Smith Patent Consulting, LLC
515 East Braddock Road, Suite B
Alexandria, VA 22314
Telephone: (703) 549-7691
Facsimile: (703) 549-7692

Name: Chalin A. Smith
Title: Attorney for Applicant
Registration No. 41,569

CUSTOMER NUMBER 31,496